◊◊ Please replace page 47, line 18-page 48, line 8, with the following:

Individual colonies are selected, cut with AsuII and BamHI, and the size of the AsuII/BamHI fragment determined. Colonies in which both the primer 1 and primer 2 sequences are correctly inserted are further amplified, an cut with AsuII and BamHI to produce the gene activation construct

cgaagcgaggcagccagcgagggagagagcgagcgggcgagccggagcgaggaaATCGAAGGTTCGAATCCTTC
CCCCACCACCATCACTTTCAAAAGTCCGAAAGAATCTGCTCCCTGCTTGTGTGTTGG
AGGTCGCTGAGTAGTGCGCGAGTAAAATTTAAGCTACAACAAGGCAAGGCTTGACC
GACAATTGCATGAAGAATCTGCTTAGGGTTAGGCGTTTTGCGCTGCTTCGCGATGTA
CGGGCCAGATATACGCGTTGACATTGATTATTGACTAGTTATTAATAGTAATCAATT
ACGGGGTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTA
AATGGCCCGCCTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGAC
GTATGTTCCCATAGTAACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGACTA
TTTACGGTAAACTGCCCACTTGGCAGTACATCAAGTGTATCATATGCCAAGTACGCC
CCCTATTGACGTCAATGACGGTAAATGGCCCGCCTGGCATTATGCCCAGTACATGAC
CTTATGGGACTTTCCTACTTGGCAGTACATCTACGTATTAGTCATCGCTATTACCATG
GTGATGCGGTTTTGGCAGTACATCAATGGGCGTGGATAGCGGTTTGACTCACGGGGA
TTTCCAAGTCTCCACCCCATTGACGTCAATGGGAGTTTGTTTTGGCACCAAAATCAA
CGGGACTTTCCAAAATGTCGTAACAACTCCGCCCCATTGACGCAAATGGGCGGTAG
GCGTGTACGGTGGGAGGTCTATATAAGCAGAGCTCTCTGGCTAACTAGAGAACCCA
CTGCTTACTGGCTTATCGAAATTAATACGACTCACTATAGGGAGACCCAAGCTTGGT
ACCGAGCTCGGATCgatctgggaaagcgcaagagagagcgcacacgcacacacccgccgcgcgcactcgg (SEQ ID NO: 25)

In this construct, the flanking primer 1 and primer 2 sequences provide the recombination region which permits the insertion of the CMV promoter in front of the coding sequence for the human *Shh* gene. Other heterologous promoters (or other transcriptional regulatory sequences) can be inserted in a genomic *hedgehog* gene by a similar method.

◊◊ Please replace the first complete paragraph on page 60 with the following:

In an illustrative embodiment, the *ptc* therapeutic can be an antisense construct for inhibiting the expression of *patched*, e.g., to mimic the inhibition of *patched* by *hedgehog*. Exemplary antisense constructs include:

C3

5'-GTCCTGGCGCCGCCGCCGCCGTCGCC (SEQ ID NO: 26)

5'-TTCCGATGACCGGCCTTTCGCGGTGA (SEQ ID NO: 27)

5'-GTGCACGGAAAGGTGCAGGCCACACT (SEQ ID NO: 28)

◊◊ Please replace the first complete paragraph on page 69 with the following:

RNA was isolated from cells and tissue using Trizol (Gibco/BRL) as prescribed by the manufacturer. Genomic DNA was removed from the RNA by incubation with 0.5 units of Dnase (Gibco/BRL, Cat # 28068-015) at room temperature for 25 minutes. The solution was heated to 75 C for 20 minutes to inactivate the DNase. Reverse transcription was carried out using random hexamer and MuLV reverse transcriptase (Gibco/BRL) as suggested by the manufacturer. All the quantitative RT-PCR internal controls, or mimics, were synthetic single stranded DNA oligonucleotides corresponding to the target sequence with an internal deletion from the central region (Oligos, Etc.; Wilsonville, OR). For actin, target = 280 bp, mimic = 230 bp; for *ptc*, target = 354 bp, mimic = 200 bp. PCR was performed using the Clontech PCR kit. For actin: annealing temperature 64 °C, oligos GGCTCCGGTATGTGC (SEQ ID NO: 29), GGGGTACTTCAGGGT (SEQ ID NO: 30). For *ptc*: annealing temperature 72 °C, oligos

C4

CATTGGCAGGAGGAGTTGATTGTGG (SEQ ID NO: 31), AGCACCTTTTGAGTGGAGTTTGGGG (SEQ ID NO: 32). In each QC-PCR reaction, four reactions were set up with equal amounts of sample cDNA in each tube and 5-fold serial dilution of mimic. Also, for each sample an aliquot of cDNA was saved and amplified along with quantitative PCR as control for contamination. PCR reactions were carried out in an MJ Research PTC-200 thermal cycler and the following cycling profile used: 95 °C for 45 seconds, 64 or 72 °C for 35 seconds, 82 °C for 30 seconds; for 40 cycles. The reaction mixtures were then fractionated by agarose electrophoresis, negative films obtained, and the films digitally scanned and quantified by area integration according to established procedures (Wang et al., 1995, and references therein). The quantity of target molecules was normalized to the competing mimic and expressed as a function of cDNA synthesized and used in each reaction.

The amended paragraphs presented above are re-stated below to reflect changes.

5'-gcgcgcttcgaaGCGAGGCAGCCAGCGAGGGAGAGAGCGAGCGGGCGAGCCGGAGC-GAGGAAatcgatgcgcgc (primer 1) (SEQ ID NO: 23)

5'-gcgcgcagatctGGGAAAGCGCAAGAGAGAGCGCACACGCACACACCCGCCGCGCG-CACTCGggatccgcgcgc (primer 2) (SEQ ID NO: 24)

Individual colonies are selected, cut with AsuII and BamHI, and the size of the AsuII/BamHI fragment determined. Colonies in which both the primer 1 and primer 2 sequences are correctly inserted are further amplified, an cut with AsuII and BamHI to produce the gene activation construct

cgaagcgaggcagccagcgagggagagagcgagcgggcgagccggagcgaggaaATCGAAGGTTCGAATCCTTC
CCCCACCACCATCACTTTCAAAAGTCCGAAAGAATCTGCTCCCTGCTTGTGTGTTGG
AGGTCGCTGAGTAGTGCGCGAGTAAAATTTAAGCTACAACAAGGCAAGGCTTGACC
GACAATTGCATGAAGAATCTGCTTAGGGTTAGGCGTTTTGCGCTGCTTCGCGATGTA
CGGGCCAGATATACGCGTTGACATTGATTATTGACTAGTTATTAATAGTAATCAATT
ACGGGGTCATTAGTTCATAGCCCATATATGGAGTTCCGCGTTACATAACTTACGGTA
AATGGCCCGCCTGGCTGACCGCCCAACGACCCCCGCCCATTGACGTCAATAATGAC
GTATGTTCCCATAGTAACGCCAATAGGGACTTTCCATTGACGTCAATGGGTGGACTA
TTTACGGTAAACTGCCCACTTGGCAGTACATCAAGTGTATCATATGCCAAGTACGCC
CCCTATTGACGTCAATGACGGTAAATGGCCCGCCTGGCATTATGCCCAGTACATGAC
CTTATGGGACTTTCCTACTTGGCAGTACATCTACGTATTAGTCATCGCTATTACCATG
GTGATGCGGTTTTGGCAGTACATCAATGGGCGTGGATAGCGGTTTGACTCACGGGGA
TTTCCAAGTCTCCACCCCATTGACGTCAATGGGAGTTTGTTTTGGCACCAAAATCAA
CGGGACTTTCCAAAATGTCGTAACAACTCCGCCCCATTGACGCAAATGGGCGGTAG
GCGTGTACGGTGGGAGGTCTATATAAGCAGAGCTCTCTGGCTAACTAGAGAACCCA
CTGCTTACTGGCTTATCGAAATTAATACGACTCACTATAGGGAGACCCAAGCTTGGT

ACCGAGGTCGGATCgatctgggaaagcgcaagagagagcgcacacgcacacacccgccgcgcgcactcgg (SEQ ID NO: 25)

In this construct, the flanking primer 1 and primer 2 sequences provide the recombination region which permits the insertion of the CMV promoter in front of the coding sequence for the human *Shh* gene. Other heterologous promoters (or other transcriptional regulatory sequences) can be inserted in a genomic *hedgehog* gene by a similar method.

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5'-GTCCTGGCGCCGCCGCCGCCGTCGCC (SEQ ID NO: 26)

5'-TTCCGATGACCGGCCTTTCGCGGTGA (SEQ ID NO: 27)

5'-GTGCACGGAAAGGTGCAGGCCACACT (SEQ ID NO: 28)

RNA was isolated from cells and tissue using Trizol (Gibco/BRL) as prescribed by the manufacturer. Genomic DNA was removed from the RNA by incubation with 0.5 units of Dnase (Gibco/BRL, Cat # 28068-015) at room temperature for 25 minutes. The solution was heated to 75 C for 20 minutes to inactivate the DNase. Reverse transcription was carried out using random hexamer and MuLV reverse transcriptase (Gibco/BRL) as suggested by the manufacturer. All the quantitative RT-PCR internal controls, or mimics, were synthetic single stranded DNA oligonucleotides corresponding to the target sequence with an internal deletion from the central region (Oligos, Etc.; Wilsonville, OR). For actin, target = 280 bp, mimic = 230 bp; for *ptc*, target = 354 bp, mimic = 200 bp. PCR was performed using the Clontech PCR kit. For actin: annealing temperature 64 °C, oligos GGCTCCGGTATGTGC (SEQ ID NO: 29), GGGGTACTTCAGGGT (SEQ ID NO: 30). For *ptc*: annealing temperature 72 °C, oligos CATTGGCAGGAGGAGTTGATTGTGG (SEQ ID NO: 31), AGCACCTTTTGAGTGGAGTTTGGGG (SEQ ID NO: 32). In each QC-PCR reaction, four reactions were set up with equal amounts of sample cDNA in each tube and 5-fold serial dilution of mimic. Also, for each sample an aliquot of cDNA was saved and amplified along with